Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 2445–2448

Tetrahedron Letters

A study of polymer-supported bases for the solution phase synthesis of glycosyl trichloroacetimidates

Jose Luis Chiara,* Lourdes Encinas and Beatriz Díaz†

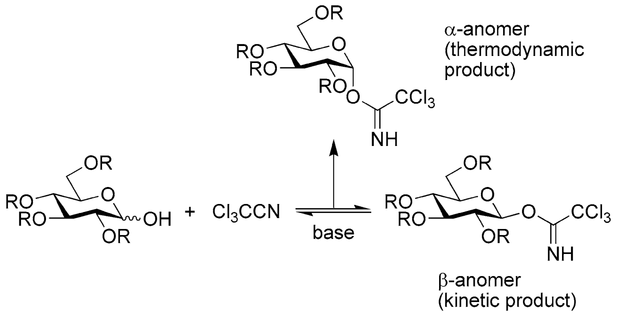
Instituto de Química Orgánica General, CSIC, Juan de la Cierva, 3, E-28006 Madrid, Spain

Received 17 December 2004; revised 8 February 2005; accepted 9 February 2005

Abstract—Polystyrene-supported strong organic bases are highly efficient reagents for the solution-phase synthesis of glycosyl trichloroacetimidates, affording quantitative yields of pure products in short reaction times after simple filtration and evaporation. Although efficiency of the different bases varies with substrate structure, polymer-bound 1,8-diazabicyclo[5.4.0]undec-7-ene was found to give the best results for all the substrates tested.

To foster advances in the emerging field of glycomics,[1] the development of improved synthetic tools for the efficient and facile assembly of complex oligosaccharides and glycoconjugates is mandatory. In spite of recent accomplishments in solid-phase[2] and enzymatic methods,[3] the synthesis of complex oligosaccharides is still a very challenging undertaking. In recent years, new solution-phase techniques have been developed to ease reaction work-up and product isolation, avoiding the pitfalls of solid-phase approaches. These techniques include the use of soluble polymer-supported methods,[4] lipophilic,[5] or fluorophilic[6] protecting groups, tagging methods for post-synthesis purification using scavenging resins,[7] solid-phase capture–release strategies,[8] sequential one-pot glycosylations,[9] and polymer-bound reagents[10] and catalysts.[11]

Glycosyl trichloroacetimidates are very efficient and widely used glycosylating reagents, which are readily prepared by base-promoted addition of an anomeric hydroxyl group to trichloroacetonitrile using either inorganic (e.g., NaH, K_2CO_3, or Cs_2CO_3) or organic (e.g., 1,8-diazabicyclo[5.4.0]undec-7-ene) bases (Scheme 1).[12] Careful chromatographic purification of crude trichloroacetimidates is usually necessary to remove all traces of base that could interfere with the subsequent acid-catalyzed glycosylation step. However, purification is often impaired by the acid lability of these glycosyl donors. As part of a project aimed at the development of practical procedures for the solution synthesis of oligosaccharides using polymer-supported reagents, we have studied the preparation of a series of glycosyl trichloroacetimidates of common hexoses in the presence of different supported bases.[13,14]



Scheme 1.

The set of bases[15] and partially protected hexoses included in this study are shown in Figure 1. Reactions were performed at room temperature under mild magnetic stirring in an air atmosphere. After the specified time, the reaction mixture was filtered, the resin was rinsed with CH_2Cl_2 and the solvent (and excess Cl_3CCN) was removed at reduced pressure. The crude was analyzed by ^1H NMR.

Each supported base was assayed with all substrates in three different solvents: CH_2Cl_2, THF, and toluene.

Keywords: Carbohydrates; Solid-supported reagents; Glycosylation.

* Corresponding author. Tel.: +34 915622900; fax: +34 915644853; e-mail: jl.chiara@iqog.csic.es

† Present address: GlaxoSmithKline S.A., P.T.M., Severo Ochoa, 2, E-28760 Tres Cantos, Madrid, Spain.

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.02.055

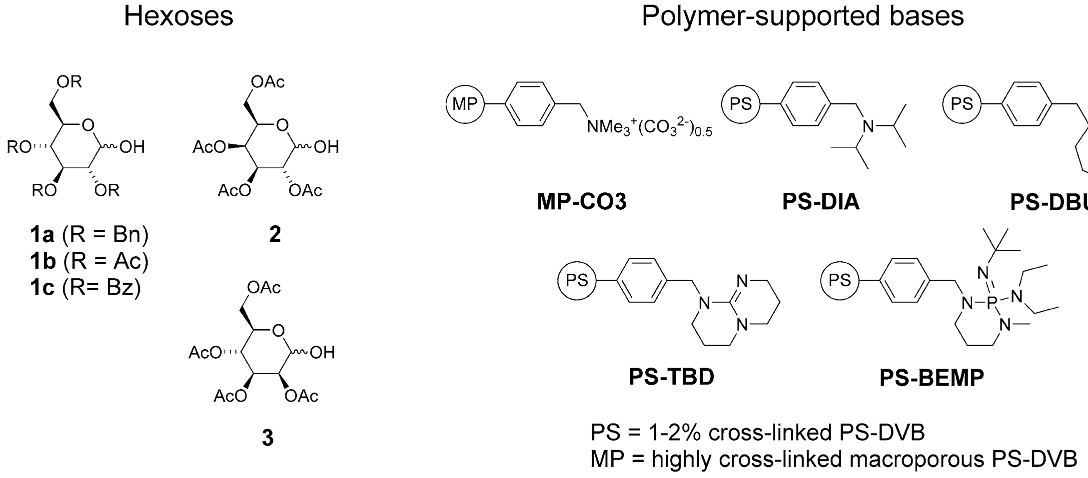


Figure 1.

The results obtained using this general procedure are presented in Table 1.

Taking 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**1a**) as a reference substrate, the performance of the different bases roughly follows the trend expected on the basis of relative base strengths (Table 1, entries 1–3 and 6).[16] Of the solvents tested, CH_2Cl_2 gives the best results and THF performs poorly in general (Table 1, entries 6–8). With regards to the bases tested, only PS-DBU and PS-BEMP efficiently promote the reaction on all substrates tested using a limited amount of base (⩽1 equiv). PS-DIA is a poor base for this reaction affording very low yields (<10%, Table 1, entries 2 and 11) of product even after extended reaction times (>24 h). MP-CO3 is only efficient for acyl-substituted hexoses (Table 1, entries 9, 10, 14, 17, and 21), what can be attributed to the increased acidity of the anomeric hydroxyl of these substrates due to the electron withdrawing effect of the acyl groups. With the exception of the D-mannopyranose derivative **3**, anomeric mixtures of glycosyl trichloroacetimidates are usually obtained. As observed under homogeneous conditions,[12] prolonged reaction times, stronger bases, or electron withdrawing groups on the hexose favor formation of increased amounts of the thermodynamically more stable α-imidate, in many cases being the exclusive product (see Scheme 1). In the case of acyl-substituted hexoses, best results are often obtained adding the base last (method B). Use of larger amounts of base gives faster

Table 1. Preparation of glycosyl trichloroacetimidates from hexoses **1**–**3** using the polymer-supported bases shown in Figure 1, under different reaction conditions

Entry	Hexose	Base (equiv)	Cl_3CCN (equiv)	Solvent	Method[a]	Time (h)	Yield (%) (α/β ratio)[b]
1	**1a**	MP-CO3 (1.5)	5.0	CH_2Cl_2	A	22	<10
2		PS-DIA (1.5)	5.0	CH_2Cl_2	A	30	N.R.
3		PS-DBU (1.5)	5.0	CH_2Cl_2	A	3.5	>99 (1:1)
4		PS-DBU (1.0)	5.0	Toluene	A	15	>99 (2:3)
5		PS-TBD (1.5)	5.0	CH_2Cl_2	A	25	20 (3:2)
6		PS-BEMP (1.0)	5.0	CH_2Cl_2	A	5.5	>99 (3:2)
7		PS-BEMP (1.5)	5.0	Toluene	A	4.5	28 (1:1)
8		PS-BEMP (1.5)	5.0	THF	A	25	N.R.
9	**1b**	MP-CO3 (1.0)	5.0	CH_2Cl_2	B	5	94 (4:1)
10		MP-CO3 (0.5)	5.0	Toluene	A	3.5	>99 (1:0)
11		PS-DIA (1.0)	5.5	CH_2Cl_2	B	36	<10
12		PS-DBU (0.5)	5.0	CH_2Cl_2	B	1.5	>99 (1:0)
13		PS-BEMP (0.5)	3.5	CH_2Cl_2	B	1.7	>99 (1:0)
14	**1c**	MP-CO3 (1.0)	5.0	CH_2Cl_2	B	4.5	>99 (9:1)
15		PS-DBU (0.5)	5.0	CH_2Cl_2	B	1.1	>99 (1:0)
16		PS-BEMP (1.0)	5.0	CH_2Cl_2	B	1.5	>99 (1:0)
17	**2**	MP-CO3 (1.0)	5.0	CH_2Cl_2	B	3.5	>99 (7:3)
18		PS-DBU (0.5)	5.0	CH_2Cl_2	B	1.5	>99 (9:1)
19		PS-TBD (1.0)	5.0	CH_2Cl_2	B	1.5	>99 (4:1)
20		PS-BEMP (0.5)	3.5	CH_2Cl_2	B	1.5	>99 (9:1)
21	**3**	MP-CO3 (0.5)	3.5	CH_2Cl_2	A	1.7	>99 (1:0)
22		PS-DBU (0.5)	5.0	CH_2Cl_2	B	1.1	>99 (1:0)
23		PS-TBD (0.5)	3.5	CH_2Cl_2	B	2.2	>99 (1:0)

[a] Method A: Cl_3CCN was added dropwise to a suspension of hexose and base in the corresponding solvent. Method B: base was added in one portion to a solution of hexose and Cl_3CCN in the corresponding solvent.

[b] Determined by ^1H NMR analysis.

reactions (Table 1, entries 3 and 4), although quantitative yields of product can be obtained in a short reaction time (<1.5 h) using substoichiometric amounts of base, if a sufficiently strong base is chosen (Table 1, entries 12, 13, 15, 18, 20, 21, and 22).

Next we tested recycling of the supported base, since it acts just as a catalyst. But, surprisingly, yields dropped by 40–90% when the resins were reused for a further imidation reaction. PS-DBU and PS-TBD, but not the strongest base PS-BEMP, could be completely regenerated for further equally efficient imidation reactions by simply washing the resin with an excess of a 1 M solution of DBU in CH_2Cl_2 and subsequent rinsing with additional clean solvent.

In summary, polystyrene-supported strong bases can be used as efficient reagents for the facile and practical preparation of glycosyl trichloroacetimidates, giving quantitative yields of pure product in short reaction times, under very mild conditions, and without any chromatographic purification. An additional advantage of the procedure is that the supported reagent can be easily regenerated and reused. Of all supported bases tested, PS-DBU is the most efficient under substoichiometric conditions and is, therefore, the reagent of choice for the general preparation of this important class of glycosyl donors.

Acknowledgments

We thank the Ministry of Education and Science of Spain for financial support (projects BQU2000-1501-C02-01 and BQU2003-03550-C03-02) and a predoctoral fellowship to L.E.

References and notes

1. (a) Khersonsky, S. M.; Ho, C. M.; Garcia, M. F.; Chang, Y. T. *Curr. Top. Med. Chem.* **2003**, *3*, 617–643; (b) Hansson, G. *Biochemist* **2003**, *25*, 11–13; (c) Ratner, D. M.; Adams, E. W.; Disney, M. D.; Seeberger, P. H. *ChemBioChem.* **2004**, *5*, 1375–1383.
2. (a) *Solid Support Oligosaccharide Synthesis and Combinatorial Carbohydrate Libraries*; Seeberger, P. H., Ed.; Wiley-Interscience: New York, 2001; (b) Seeberger, P. H. *J. Carbohydr. Chem.* **2002**, *21*, 613–643; (c) Seeberger, P. H. *Chem. Commun.* **2003**, 1115–1121.
3. Chen, X.; Liu, Z.-Y.; Zhang, J.-B.; Zheng, W.; Kowal, P.; Wang, P. G. *ChemBioChem.* **2002**, *3*, 47–53.
4. (a) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1991**, *113*, 5095–5097; (b) Yan, F.; Gilbert, M.; Wakarchuk, W. W.; Brisson, J.-R.; Whitfield, D. M. *Org. Lett.* **2001**, *3*, 3265–3268; (c) Ando, H.; Manabe, S.; Nakahara, Y.; Ito, Y. *J. Am. Chem. Soc.* **2001**, *123*, 3848–3849; (d) Geurtsen, R.; Boons, G.-J. *Eur. J. Org. Chem.* **2002**, 1473–1477; (e) Majumdar, D.; Zhu, T.; Boons, G.-J. *Org. Lett.* **2003**, *5*, 3591–3594.
5. (a) Kanie, O.; Barresi, F.; Ding, Y.; Labbe, J.; Otter, A.; Forsberg, L. S.; Ernst, B.; Hindsgaul, O. *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 2720–2722; (b) Nilsson, U. J.; Fournier, E. J. L.; Hindsgaul, O. *Bioorg. Med. Chem.* **1998**, *6*, 1563–1575; (c) Pozsgay, V. *Org. Lett.* **1999**, *1*, 477–479; (d) Pozsgay, V. *Tetrahedron: Asymmetry* **2000**, *11*, 151–172.
6. (a) Curran, D. P.; Ferritto, R.; Hua, Y. *Tetrahedron Lett.* **1998**, *39*, 4937–4940; (b) Miura, T.; Hirose, Y.; Ohmae, M.; Inazu, T. *Org. Lett.* **2001**, *3*, 3947–3950; (c) Miura, T.; Inazu, T. *Tetrahedron Lett.* **2003**, *44*, 1819–1821; (d) Miura, T.; Goto, K.; Hosaka, D.; Inazu, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2047–2051; (e) Miura, T.; Goto, K.; Waragai, H.; Matsumoto, H.; Hirose, Y.; Ohmae, M.; Ishida, H.-k.; Satoh, A.; Inazu, T. J. *Org. Chem.* **2004**, *69*, 5348–5353; (f) Manzoni, L. *Chem. Commun.* **2003**, 2930–2931; (g) Jing, Y.; Huang, X. *Tetrahedron Lett.* **2004**, *45*, 4615–4618; (h) Goto, K.; Miura, T.; Hosaka, D.; Matsumoto, H.; Mizuno, M.; Ishida, H.-k.; Inazu, T. *Tetrahedron* **2004**, *60*, 8845–8854.
7. Palmacci, E. R.; Hewitt, M. C.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4433–4437.
8. (a) Ando, H.; Manabe, S.; Nakahara, Y.; Ito, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 4725–4728; (b) Egusa, K.; Kusumoto, S.; Fukase, K. *Synlett* **2001**, 777–780; (c) Ito, Y.; Manabe, S. *Chem. Eur. J.* **2002**, *8*, 3076–3084; (d) Egusa, K.; Kusumoto, K.; Fukase, K. *Eur. J. Org. Chem.* **2003**, 3435–3445.
9. (a) Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073–12074; (b) Zhang, Z. Y.; Ollmann, I. R.; Ye, X. S.; Wischnat, R.; Baasov, T.; Wong, C. H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753; (c) Ye, X. S.; Wong, C. H. *J. Org. Chem.* **2000**, *65*, 2410–2431; (d) Valverde, S.; Garcia, M.; Gomez, A. M.; Lopez, J. C. *Chem. Commun.* **2000**, 813–814; (e) Tanaka, H.; Adachi, M.; Tsukamoto, H.; Ikeda, T.; Yamada, H.; Takahashi, T. *Org. Lett.* **2002**, *4*, 4213–4216; (f) Fraser-Reid, B.; Lopez, J. C.; Radhakrishnan, K. V.; Nandakumar, M. V.; Gomez, A. M.; Uriel, C. *Chem. Commun.* **2002**, *22*, 2104–2105; (g) Codee, J. D. C.; van den Bos, L. J.; Litjens, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947–1950; (h) Hashihayata, T.; Ikegai, K.; Takeuchi, K.; Jona, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1829–1848; (i) Amaya, T.; Takahashi, D.; Tanaka, H.; Takahashi, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1833–1836; (j) Tanaka, H.; Adachi, M.; Takahashi, T. *Tetrahedron Lett.* **2004**, *45*, 1433–1436; (k) Huang, X. F.; Huang, L. J.; Wang, H. S.; Ye, X. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221–5224.
10. (a) Kirschning, A.; Jesberger, M.; Schoenberger, A. *Org. Lett.* **2001**, *3*, 3623–3626; (b) Jaunzems, J.; Hofer, E.; Jesberger, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1166–1170; (c) Jaunzems, J.; Sourkouni-Argirusi, G.; Jesberger, M.; Kirschning, A. *Tetrahedron Lett.* **2003**, *44*, 637–639; (d) MacCoss, R. N.; Brennan, P. E.; Ley, S. V. *Org. Bioorg. Chem.* **2003**, *1*, 2029–2031; (e) Jaunzems, J.; Kashin, D.; Schonberger, A.; Kirschning, A. *Eur. J. Org. Chem.* **2004**, 3435–3446.
11. For the first example of glycoside synthesis using a solid-phase supported reagent, see: Paulsen, H.; Lockhoff, O. *Ber.* **1981**, *114*, 3102–3114; For recent reports, see: (a) Toshima, K.; Kasumi, K.; Matsumura, S. *Synlett* **1999**, 813–815; (b) Toshima, K.; Nagai, H.; Matsumura, S. *Synlett* **1999**, 1420–1422; (c) Yoshizaki, H.; Fukuda, N.; Sato, K.; Oikawa, M.; Fukase, K.; Suda, Y.; Kusumoto, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1475–1480; (d) Nagai, H.; Kawahara, K.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2001**, *42*, 4159–4162; (e) Nagai, H.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2002**, *43*, 847–850.
12. Schmidt, R. R. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123.
13. This work has been communicated in preliminary form at the 2004 Gordon Research Conference on Combinatorial Chemistry, Oxford, UK, Aug 22–27, 2004.

14. For a recent report on the use of Dowex 1-X8 OH^- resin for imidation of a glucosamine derivative, see: Yoshizaki, H.; Fukuda, N.; Sato, K.; Oikawa, M.; Fukase, K.; Suda, Y.; Kusumoto, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1475–1480; For a very recent example of imidation of an unusual 2-deoxy amino sugar using PS-DBU, see: Ohashi, I.; Lear, M. J.; Yoshimura, F.; Hirama, M. *Org. Lett.* **2004**, *6*, 719–722; When this work was in preparation, the use of PS-TBD in a one-pot glycosylation protocol was published: Oikawa, M.; Tanaka, T.; Fukuda, N.; Kusumoto, S. *Tetrahedron Lett.* **2004**, *45*, 4039–4042.

15. PS-CO3 (2.8–3.5 mmol/g) and PS-DIA (3.6 mmol/g) were purchased from Argonaut, PS-TBD (2.6 mmol/g) was from Aldrich, PS-BEMP (2.6 mmol/g) was from Fluka, and PS-DBU (2.7 mmol/g) was prepared following a literature procedure: Tomoi, M.; Kato, Y.; Kakiuchi, H. *Makromol. Chem.* **1984**, *185*, 2117–2124.

16. As an indication of the relative base strength of the different supported bases used in this study, the pK_a values reported for the conjugated acids of their corresponding non-supported analogs are as follows: diisopropylethylamine: 18.1 (MeCN, 25 °C);[17] DBU: 24.13 (MeCN, 25 °C);[18] 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD): 25.44 (MeCN, 25 °C),[19] 24.70 (MeCN, 25 °C);[20] 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP): 27.63 (MeCN, 25 °C).[19] To our knowledge, there is no pK_a value reported for HCO_3^- ion in MeCN, and the value 10.25 (H_2O, 25 °C),[21] should be considered as a lower limit.

17. Kelly-Rowley, A. M.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **1995**, *117*, 3438–3447.

18. Kaliurand, I.; Rodima, T.; Leito, I.; Koppel, I. A.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 6202–6208.

19. Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435–2454.

20. Gierczyk, B.; Wojciechowski, G.; Brzezinski, B.; Grech, E.; Schroeder, G. *J. Phys. Org. Chem.* **2001**, *14*, 691–696.

21. *CRC Handbook of Chemistry and Physics*; Lide, D. R., Ed., 82nd ed.; CRC: Boca Raton, 2002.